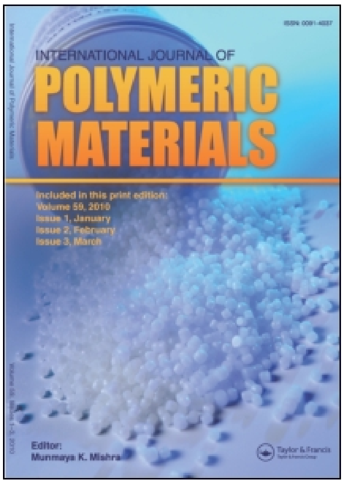

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Synthesis of Ultra-high Weight Average Molecular Mass of Poly-L-lactide

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High purity in high yield L-lactide was prepared using a new purification method, and poly-L-lactide (PLLA) with ultra-high weight average molecular mass and narrow polydispersity index was synthesized by ring-opening polymerization. The effects of the purification method on the purity and yield of L-lactide were investigated, and the influences of initiator concentration, polymerization temperature and polymerization time on the weight average molecular mass of PLLA were also studied. A synthetic purification method involving a water bath and two times recrystallization could improve the purity of L-lactide to 100%. The yield of L-lactide reached 40.6% and increased 12.1% compared with the recrystallization method. Poly-L-lactide with a weight average molecular mass of about 102.4×10^4 *and a polydispersity index of 1.16 was obtained when polymerization was conducted with molar ratio of monomer to initiator ([M]/[I]) of 12000 for 24 h at 140°C.*

Keywords: L-lactide, poly-L-lactide, purification, synthesis, ultra-high weight average molecular mass

INTRODUCTION

Poly-L-lactide (PLLA) is the most commonly used biodegradable polymer in surgery, especially in osteosynthesis [1,2], and in general is considered safe for clinical use [3], although unexpected phenomena such as long degradation periods are not uncommon [4]. One aim for

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the use of these degradable polymers is the prevention of repeated surgery for the patient [5]. Additional areas for the use of biodegradable polymers are drug delivery and, more recently, tissue engineering [6,7]. Especially in the latter field, the use of biodegradable matrices is of importance since besides the structural support these polymers also function as carriers of living cells. Ring-opening polymerization of lactides is important to obtain high relative molecular mass. However, purity of the monomer, catalyst, reaction temperature and reaction time are important influencing factors on the relative molecular mass of PLLA and its distribution [8]. The key step in the preparation of PLLA is high purity lactide. Although many papers on the synthesis of PLLA have been published [9,10], there are still many problems on how to control the mechanical properties, recrystallization and degradation rate of PLLA [11,12]. So it is necessary to study the purification of L-lactide and polymerization conditions to obtain relative high molecular mass PLLA.

In this article, the influences of purifying methods on L-lactide, ultra-high weight average molecular mass PLLA was synthesized by ring-opening polymerization, and the relationships between weight average molecular mass of poly-L-lactide and polymerization conditions are investigated.

EXPERIMENTAL

Preparation of L-lactide

The preparation of LLA was achieved under atmospheric pressure and low pressure, in three stages. In the first stage, some L-lactic acid was placed in a flask with a distillation head. Under atmospheric pressure, the L-lactic acid was dehydrated at 135–150°C for 3–4 h. Second, under low pressure (2.5–8.0 kPa), L-lactic acid was heated and melted at 150–160°C for 2–3 h while the temperature increased gradually. The condensation reaction took place at this stage. At last, the catalyst stannous octoate, 1% (mass fraction) to the oligomer, was added to the flask. Depolymerization of the oligomer to produce the cyclic L-lactide dimer was carried out under reduced pressure (about 0.027 kPa). Crude L-lactide was obtained by controlling the depolymerization temperature between 180 and 220°C.

Purification of L-lactide

The crude L-lactide was purified by the synthetic purifying method and recrystallization method, separately. The first purification consists of water bath and two times recrystallization. The molten L-lactide was poured into water and stirred constantly, and the temperature was reduced to ambient temperature as fast as possible. The mixture was agitated for about 1 h and a slurry was obtained. L-lactide was separated from the mixture using a Buchner funnel. After drying in a vacuum oven at 40°C, the LLA was recrystallized from ethyl acetate twice. The dried LLA was stored in a desiccator with P_2O_5. In the second method the crude lactide was recrystallized from ethyl acetate six times. Then it was dried in a vacuum oven, and stored in a desiccator with P_2O_5.

Polymerization of L-lactide

Poly-L-lactide (PLLA) was polymerized in a way similar to that described in the literature [9]. Briefly, PLLA was obtained by ring-opening polymerization of L-lactide using tin octoate as an initiator. Ampoules for polymerization were dried in an oven at 400°C for 4 h. Then, they were loaded with freshly recrystallized L-lactide and tin octoate toluene solution at monomer/initiator molar ratios $[M]/[I] = 6000–14000$, sealed under high vacuum, and left in the oven at 120–160°C for the material to polymerize.

Measurements

The purity of L-lactide was measured using gas chromatogram and mass spectrum on GCMS2QP2010 (Shimadzu Company, Japan). The optical purity of LLA was measured by WZZ-2A polarimeter at 22°C with benzene as a solvent, and the wavelength of Na was 589 nm. IR spectra of L-lactide were measured using KBr pellets on Nicolet 2210. The weight average molecular mass was measured using a Waters 510 instrument with Shodex KF-800 columns, and the data processing software was Waters Millennium32. Samples were measured at 35°C with chloroform as an eluent at a flow rate of $1.0\,\mathrm{mL \cdot min^{-1}}$. The molecular weight was calibrated relative to polystyrene standards.

RESULTS AND DISCUSSION

Purification and Characterization of L-lactide

Optical Purity of L-lactide

The specific rotatory power of standard LLA is -297° [13]. The specific rotatory power of LLA prepared in our laboratory was

-298.42°, which is 1.42° higher than the standard. This result demonstrates that the LLA prepared in our laboratory is of optical purity. Using the prepared LLA as standard, the optical rotation of LLA obtained in every purifying procedure can be detected. And its optical purity can be calculated.

IR Spectrum Analysis of L-lactide

IR spectra of crude and purified LLA are shown in Figure 1. Referring to the IR spectrum of lactic acid [14], lactic acid has a broad and strong absorption peak in the range of 3500–2500 cm^{-1}. It is shown in Figure 1(a) that the crude lactide has the same band. Comparing the same band of lactide and the lactic acid suggests that the crude lactide contains remnant lactic acid, water and probably oligomer. As shown in Figure 1(b), there is a strong absorption peak of ester-carbonyl group at 1754.18 cm^{-1} and the absorption peaks of $-CH_3$ at 2933.69 cm^{-1} and 1452.18 cm^{-1}. There is a deformation vibration of C–H in the lactide ring at 932.76 cm^{-1}. It is very similar to the absorption peak of C–H of cyclohexane because of the special six atom ring structure of LLA. Absorption peak of C–O is at 1268.18 cm^{-1}; Absorption of –C–O–C– is at 1093.56 cm^{-1}; vibration flex peaks of C–H are at 2996.39 cm^{-1} and 2933.69 cm^{-1}.

Gas Chromatography/Mass Spectrometry

Gas chromatogram and mass spectrogram of LLA purified by the synthetic purifying method are shown in Figures 2 and 3. In Figure 2, there is a peak at 8.204 min. The ions are detected by mass spectrometry. In Figure 3, the largest ratio of mass to electron charge (m/e) is 144. That means this peak is molecular ion (M+) peak and the relative molecular mass of the specimen is 144. Meanwhile there are no isotopic peaks of N, S, halogen and so on. This suggests that the specimen consists of three elements, which are C, H and O. The m/e of the base peak is 56. This comes from the breakage of C–O of ester bond. Compared with the standard data, the specimen is LLA. The suggests that the LLA purified by the synthetic purifying method is of high purity.

Effects of Purifying Method on Purity and Yield of LLA

The effects of recrystallization on the purity and yield of LLA is shown in Table 1. It can be seen that the optical purity of LLA is 99.59% when purified by recrystallization six times, which means recrystallization can purify LLA, but the loss rate of LLA is high because of the dissolution in the solvent. From Table 1, it can be seen that the yield of LLA is only 28.5% after six times recrystallization.

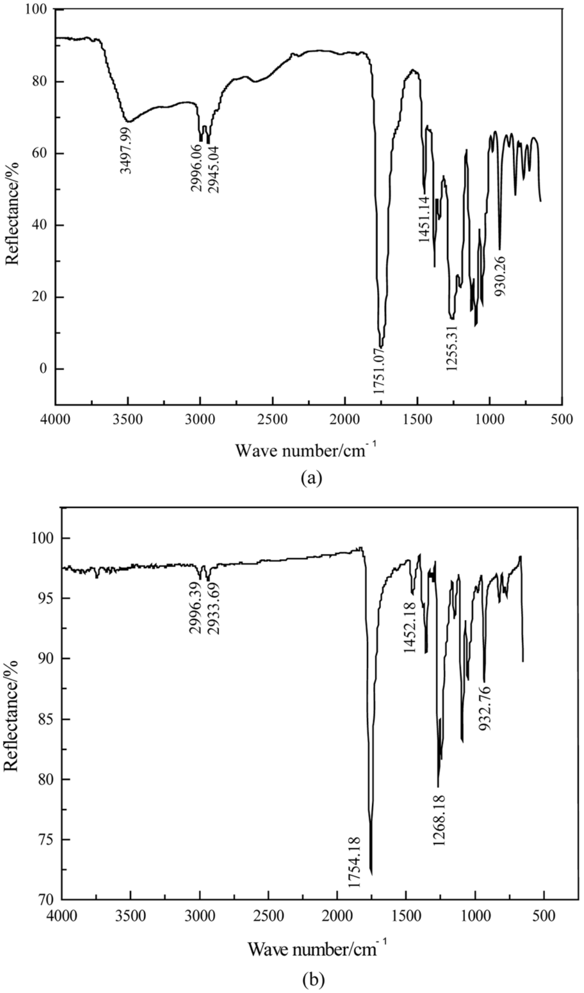

FIGURE 1 IR spectrum of LLA: (a) unpurified; (b) purified.

The process of recrystallization is very troublesome, so this method is only applicable to laboratory, not commercial, processes.

Table 2 shows the effect of the synthetic purification method on purity and yield of LLA. It can be seen that LLA of 100.0% can be obtained by the synthetic purifying method, and the yield is 40.6%. It may be explained that the hydrolysis speed of meso-lactide is greater than that of LLA [15]. So it is very easy to eliminate the great mass of meso-lactide by washing with water. Compared to the recrystallization method, the synthetic purifying method not only

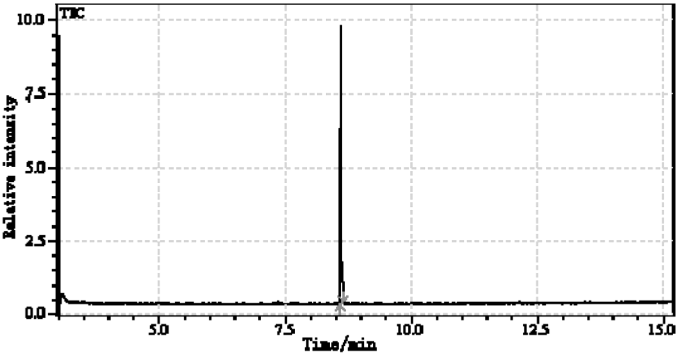

FIGURE 2 Gas chromatogram of purified LLA.

simplifies the purifying process but also greatly, increases the yield of LLA, and the yield of LLA increases by 12.1%. It is clear that the synthetic purifying method not only cuts the cost but also reduces the amount of solvent, which is beneficial to the procedure, and makes the commercial process possible.

Preparation of PLLA

Effect of Polymerization Temperature on Weight Average Molecular Mass

Figure 4 shows the weight average molecular mass of PLLA and polydispersity index as a function of the polymerization temperature

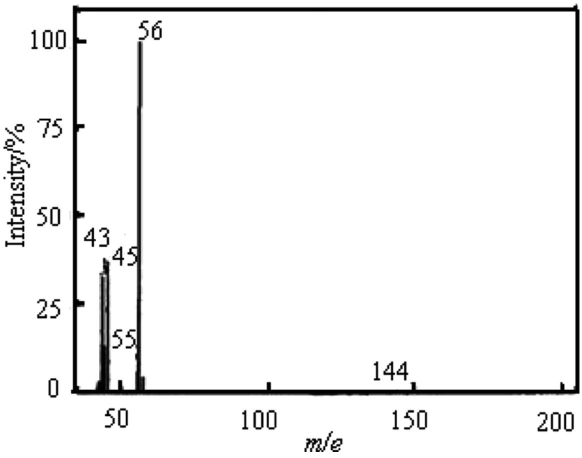

FIGURE 3 Mass spectrogram of purified LLA.

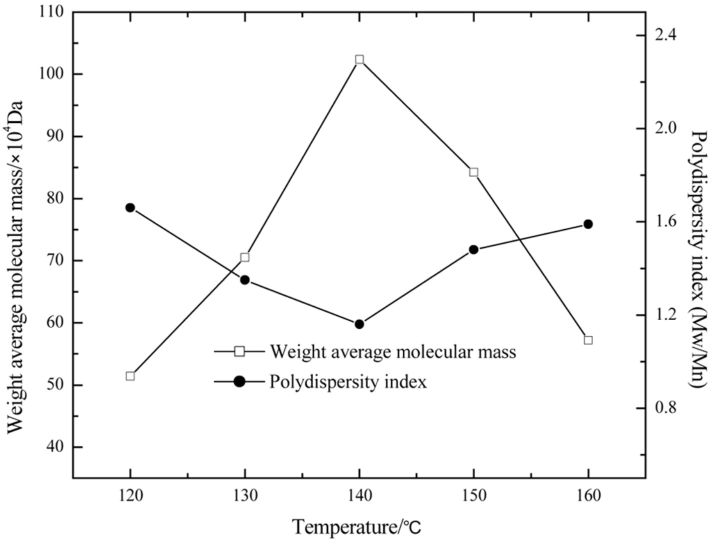

FIGURE 4 Weight average molecular mass and polydispersity index as a function of the polymerization temperature.

when polymerization is conducted at [M]/[I] molar ratio of 12000 for 24 h. It is clearly seen in Figure 4 that poly-L-lactide with a weight average molecular mass of about 102.4×10^4 is obtained at 140°C and the distribution index is 1.16. When the temperature is too high, the depolymerization of PLLA is accelerated, so that the weight average molecular mass becomes lower and the polydispersity index becomes lager. However, with lower temperature, polymerization and monomer conversion are slow, the polydispersity index becomes larger and the molecular distribution becomes broader because of the presence of more monomer.

TABLE 1 Effects of Recrystallization on Purity and Yield of LLA

Times of recrystallization	Specific rotatory power of LLA/(°)	Mass fraction of LLA/(%)	Mass fraction of meso-lactide/(%)	Yield/ (%)
1	−272.21	91.22	8.78	78.4
2	−277.93	93.13	6.87	63.8
3	−284.56	95.36	4.64	52.6
4	−290.28	97.27	2.83	38.1
5	−292.99	98.18	1.92	33.0
6	−297.21	99.59	0.41	28.5

TABLE 2 Effects of Synthetic Purifying Method on Purity and Yield of LLA

Purifying	Specific rotatory power of LLA/(°)	Mass fraction of LLA/(%)	Mass fraction of meso-lactide/(%)	Yield/ (%)
Washing with water	−296.93	99.50	0.50	73.8
First recrystallization	−297.82	99.80	0.20	43.2
Second recrystallization	−298.42	100	—	40.6

Effect of Polymerization Time on Weight Average Molecular Weight

Figure 5 illustrates the weight average molecular mass and polydispersity index as a function of polymerization time at 140℃ at [M]/[I] ratio of 12000. It can be seen that the weight average molecular mass of poly-L-lactide increases with polymerization time at the initial stage of polymerization, followed by a decrease in the subsequent stages. However, the polydispersity index first decreases, then increases as the reaction continues. Increasing of the weight average molecular mass with polymerization time reveals that ring-opening polymerization of lactide proceeds not only by a chain reaction but also by a step-growth reaction mechanism, as reported for ring-opening

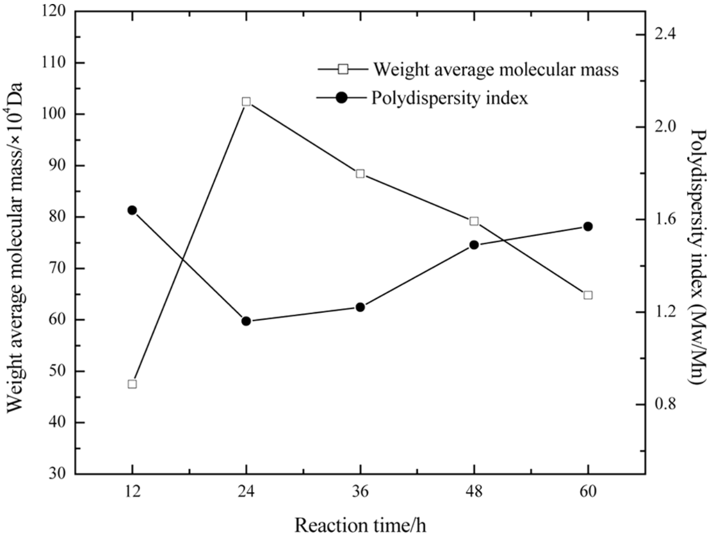

FIGURE 5 Weight average molecular mass and polydispersity index as a function of polymerization time.

polymerization of other types of cyclic esters [16]. The decrease of the weight average molecular mass and the increase of the polydispersity index at long polymerization times are attributed to the thermal depolymerization of the resultant polymers.

Effect of Concentration of Catalyst on the Weight Average Molecular Mass

Figure 6 shows the weight average molecular mass and polydispersity index as a function of stannous octanoate concentration, at 140°C for 24 h. As shown in Figure 6, the highest weight average molecular mass of polymer can be obtained at about [M]/[I] of 12000. The molecular weight of poly-l-lactide increases firstly and then decreases with the increasing of [M]/[I] molar ratio. However, the value of the polydispersity index goes in the opposite direction. This may be explained as follows: when [M]/[I] ratio is small, there are more active sites and the number of propagating monomers per active site is small, therefore, the molecular mass of poly-l-lactide is also small and the polydispersity index is large. On the other hand, when [M]/[I] ratio is high, there are fewer active sites and the conversion of the monomer is low, so that the molecular mass of poly-l-lactide is large and the polydispersity index is small.

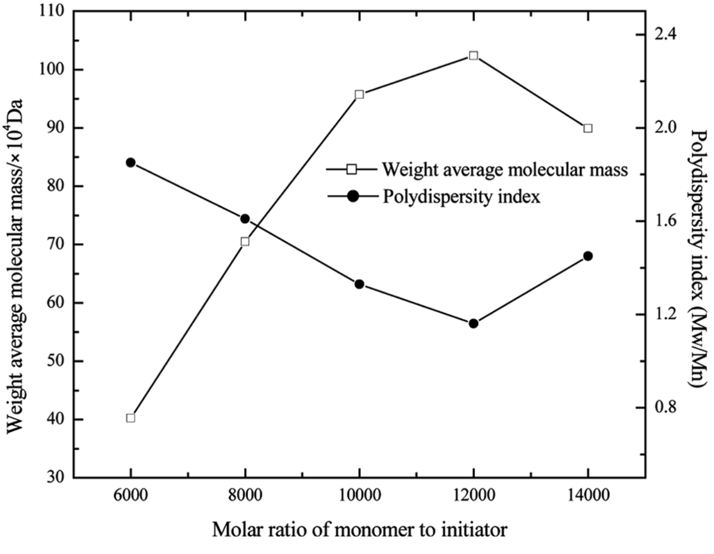

FIGURE 6 Weight average molecular mass and polydispersity index as a function of concentration of catalyst.

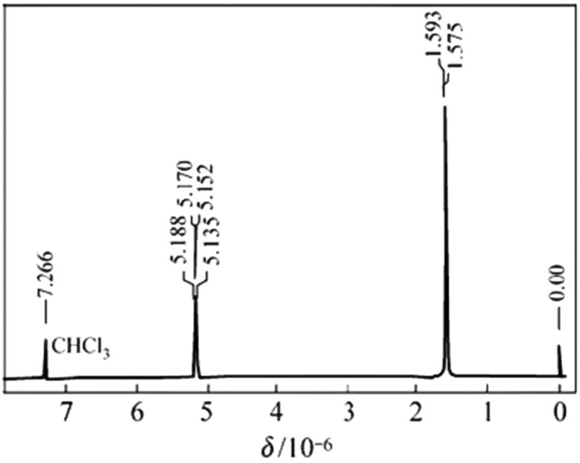

FIGURE 7 ^{1}H-NMR spectrum of PLLA.

Characterization of PLLA by ^{1}H-NMR

The ^{1}H-NMR spectrum of PLLA (seen in Figure 7) shows the signal at $\delta = 5.15$ ppm attributed to methane protons (quartet, $J = 6.7$ Hz), and at about $\delta = 1.57$ ppm attributed to methyl protons (doublets). The signal of the methyl protons of the polymer is slightly up-field relative to that of the cyclic dimer probably due to the ring opening and linear chain conformation. These results correspond well to those reported in the literature [17].

CONCLUSIONS

High purity L-lactide in a yield of 40.6% can be obtained by using a synthetic purifying method, and the yield increases 12.1% compared with the recrystallization method. In the process of the synthetic purifying method, a great deal of organic solvent is saved, and the purification technology is simplified. Polymerization conditions have effects on weight average molecular mass. In the optimal condition, poly-L-lactide with a ultra-high weight average molecular mass of about 102.4×10^4 could be obtained, with a distribution index of 1.16.

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